Writing for orphan drugs:
A compass to navigate document types and regional requirements

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Abstract
Medical writing for rare diseases encompasses the development of various regulatory documents that are required to obtain orphan drug designation and marketing authorisation for treatments targeting rare conditions. Effective planning and close collaboration with key stakeholders are essential to navigate regional regulatory requirements and address unmet patient needs, ultimately facilitating the approval of treatments for rare diseases.

Introduction
Rare diseases are serious, chronic, progressive diseases that affect a small number of individuals. The definition of a rare disease based on its prevalence is not universal and varies across jurisdictions. In Europe, a disease is considered to be rare when it affects fewer than 5 per 10,000 people.[1] It is estimated that about 36 million people live with a rare disease in Europe,[1] which represents approximately 5% of the European population.

The first compilation of diseases with low prevalence dates back to 1581, with the publication of *Medicinalium observationum exempla rara, recognita et aucta* by Rembert Dodoens.[2] Five hundred years later, the advances in scientific

knowledge have led to the identification of between 6,000 and 8,000 rare diseases, with new diseases regularly described in medical literature. Approximately 80% of rare diseases have a genetic cause, 70% have a paediatric onset, and about 95% lack approved treatments.[3,4] Because of the lack of approved treatments, the off-label use of prescribed drugs is common among patients with these conditions.

Several interrelated factors contribute to the deficit of treatments for rare diseases:

- **High development costs** with limited potential for return on investment due to small market size.
- **Long development timelines** due to the prolonged trial recruitment periods in small populations.
- **Lack of or poor understanding** of the pathophysiological mechanisms and the natural history of these diseases.
- **Difficulty in generating confirmatory evidence** using traditional trial designs due to the small and usually heterogeneous patient population. In this scenario, innovative designs and novel endpoints are required for obtaining substantial evidence of efficacy and safety.
- **Limited collaboration and data sharing** through registries and collaborative networks and databases hinder the collection of robust data to inform and optimise clinical trial design.

Regulatory agencies play a crucial role in supporting the development of drugs for rare diseases through various mechanisms and programmes designed to address the unique challenges associated with these conditions. One of these mechanisms is the orphan drug status that incentivises the development of treatments for rare diseases by providing benefits such as scientific advice and market exclusivity. The EMA offers several programmes to expedite drug development and approval, including conditional marketing authorisation, marketing authorisation under exceptional circumstances, or the PRIority MEdicines (PRIME) scheme. Similarly, the US FDA provides programmes such as Fast Track, Priority Review, Breakthrough Therapy Designation, and Accelerated Approval.

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Overview of orphan drug status

The process for applying for orphan drug status varies between regions and countries. An overview of application procedures and content is provided for the EU, US, and Japan (refer to Table 1); other jurisdictions with orphan drug legislation include Singapore, Australia, South Korea, and Taiwan.[5] Some regions and countries collaborate when evaluating orphan drug applications; for example, EMA encourages simultaneous applications to the US and Japan.[6] Presubmission meetings may be requested before applying for orphan drug status, in which case the medical writer is likely to be involved in the preparation of one or more briefing packages as well as the orphan drug application.

In the EU, an application for orphan drug designation (ODD) is made by submitting a form via the EMA Regulatory & Scientific Information Management Platform (IRIS). The scientific part of the

Table 1. Summary of orphan drug status in selected regions/countries

Country/ region (agency)	Prevalence criterion	Scientific advice	Financial incentives	Other incentives
EU (EMA)[13]	< 5 in 10,000 people affected in the EU	Yes[a] – Protocol Scientific Advice	• Reduced fees for protocol assistance and regulatory activities	• Potential access to conditional approval • Market exclusivity after approval (10 years; 12 years for medicines that also have complied with an agreed PIP)
US (FDA)[14]	< 200,000 people affected in the US	Yes[a]	• Exemption from scientific advice fees • Tax credits for qualified clinical trials • Grant funding for research[b]	• Potential market exclusivity after approval (7 years)
Japan (NIBIO, MHLW, PMDA)[15]	< 50,000 people affected in Japan	Yes, including PMDA priority consultation system	• Reduced fees for PMDA priority consultation system • Subsidies for development costs; tax credits for trial expenses	• Priority review • Extension of re-examination period (10 years for drugs; 7 years for devices)

Abbreviations: EMA, European Medicines Agency; EU, European Union; FDA, Food and Drug Administration; MHLW, Ministry of Health, Labour and Welfare; NIBIO, National Institute of Biomedical Innovation; PIP, paediatric investigation plan; PMDA, Pharmaceuticals and Medical Devices Agency; US: United States.

[a] Recommended parallel submission with US FDA and EU EMA.

[b] Orphan drug status is not required for grant funding but is encouraged.

Table 2. Sections of the EMA Orphan Drug Designation Application Form[6,7]

Section	Overall topic	Details of content
A	Description of the condition	A1. Details of the condition (definition, aetiology, specific characteristics, classification, diagnosis, and symptoms) A2. Proposed orphan indication. A3. Medical plausibility (active substance, description of the medicinal product and information on the plausibility of the orphan condition including supportive data). A4. Justification of the life-threatening or debilitating nature of the condition
B	Prevalence of the condition	B1. Prevalence of the orphan disease or condition in the EU B2. Prevalence and incidence of the condition in the EU
C	Potential for return on investment	C1. Grants and tax incentives C2. Past and future costs C3. Production and marketing costs C4. Expected revenues C5. Certification by registered accountant
D	Other methods for diagnosis, prevention or treatment of the condition	D1. Details of any existing diagnosis, prevention, or treatment methods D2. Justification as to why methods are not satisfactory D3. Justification of significant benefit
E	Description of the stage of development	E1. Summary of the development of the product E2. Details of current regulatory status and marketing history in the EU and non-EU countries

Abbreviations: EMA, European Medicines Agency; EU, European Union.

Note: ■ shaded sections are those for which the medical writer is most likely to act as the author; ■ non-shaded sections are those for which the medical writer collaborates with other functions.

form, which is the most likely to require medical writing input, consists of five sections designated A to E as shown in Table 2, plus a bibliography (Section F). Per EMA guidance, Sections A to E should generally be a maximum of 30 pages.[7] For Sections A, D, and E, the latest Investigator's Brochure and any recent briefing packages are likely to provide useful information as a starting point. Key collaborators for these sections include clinical science, regulatory affairs, and biostatistics. Section B is likely to require specialist epidemiology input. Section C is typically only required if the usual prevalence requirement of less than 5 people per 10,000 in the EU is not met and the application is instead being made based on insufficient return to justify the necessary investment.

In the US, the requirements of an orphan drug application are set out in Title 21 of the US Code of Federal Regulations (CFR) Section 316.20(b), as summarised in Table 3. The length is expected to be approximately 20 to 30 pages, similar to the EMA application, and medical writers are likely to work on similar content. The application can be submitted using Form FDA 4035. Use of this form is optional as long as the equivalent information is included; however, the form contains useful guidance on the quantity of text and type of information required. Further guidance is available in an FDA webinar.[8]

In Japan, orphan designation is based on Article 77-2 of the Pharmaceutical Affairs Law and applications are made via the Ministry of Health, Labour, and Welfare. The application can be submitted using the Application Form for Orphan Drug/Medical Device Designation Consultation; as with the US, use of the form is optional but recommended. Note that the form is in Japanese and the application must be submitted in the local language; a copy of the form annotated in English is also available.[9] A summary of the required content is provided in Table 4.

Considerations for writing orphan drup applications

As shown in Tables 2, 3, and 4, there is substantial overlap among jurisdictions in terms of orphan drug application content. It can therefore be efficient to create a single core document containing information that can be repurposed for individual applications, such as details of the drug, the disease background, justification for why the drug is needed, and supporting data. The latest Investigator's Brochure and any recent briefing packages are likely to provide useful content as a starting point.

Prevalence data need to be researched and written separately for each application as it is specific to each region/country; specialist epidemiology input is recommended.

Content on why existing treatments are insufficient may also need to be adapted for different jurisdictions, as each market may have a different range of authorised treatments. The approval dates for widely authorised treatments are also likely to differ. It can be useful to include

Table 3. Overview of required content for a US Orphan Drug Application[8,16]

Subsection of 21 CFR Section 316.20(b)	Overall topic	Details of content
1	Identity of the rare disease or condition	• Statement that the sponsor requests ODD for a rare disease or condition • Specific identify of the disease or condition
2	Administrative information	• Sponsor contact details • Generic and trade name of the drug if available, or the chemical name or a meaningful descriptive name of the drug • Name and address of the source of the drug if it is not manufactured by the sponsor
3	Disease background	• Description of the rare disease or condition for which the drug is being or will be investigated • Proposed use of the drug • Reasons why such therapy is needed
4	Description of the drug	• Active moiety (small molecules) or features of molecular structure (macromolecules) • Physical and chemical properties • Scientific rationale for the use of the drug for the rare disease or condition, including all relevant data
5	Clinical superiority (if applicable)	When is it applicable? If the drug is a "same drug" as an already approved drug[a] for the same rare disease or condition for which the sponsor is requesting an ODD. What must be included? An explanation of why the proposed variation may be clinically superior to the first drug.
6	Orphan subset (if applicable)	When is it applicable? If the ODD request is for a drug for only a subset of persons with a particular disease or condition that otherwise affects 200,000 or more people. What must be included? A justification that, due to one or more properties of the drug, the remaining people with the disease or condition would not be appropriate candidates for use of the drug.
7	Regulatory status/ marketing history	A summary of the regulatory status and marketing history of the drug in the US and other countries. Any adverse regulatory actions taken against the drug in any country.
8	Population estimate	Documentation, with appended authoritative references, to demonstrate that: (i) Fewer than 200,000 people in the US have the disease or condition, or would otherwise receive the drug per year if it is a vaccine or diagnostic OR (ii) If 200,000 or more people in the US are affected by the disease or condition, or would otherwise receive the drug per year, there is no reasonable expectation that costs of research and development of the drug for the indication can be recovered by sales of the drug in the US

Abbreviations: CFR, Code of Federal Regulations; ODD, orphan-drug designation; US, United States.

[a] The concept of "same drug" is defined in 21 CFR 316.3(b)(14)

appendices in the core document detailing the significant benefits over each existing treatment; content from the relevant appendices can then be included in each application.

The timing of each orphan drug application may need to be carefully considered in the context of the marketing application timing, as some countries/regions may require the marketing application to be filed within a certain period of time after the ODD is approved.

Documents for orphan drugs at the time of applying for approval

Medical writers should be prepared to support additional orphan-drug-related documents in the lead up to submission of an EMA marketing authorisation application.

During the review of a marketing authorisation, the EMA assesses whether a drug continues to meet the criteria for maintaining its orphan status. An orphan maintenance assessment report must be submitted to provide relevant information; exact timing of the submission depends on whether the review is

Table 4. Overview of required content for an orphan drug application in Japan[9]

Overall topic	Details of content
Product details	• Name of active substance • Composition of investigational product • Outline of manufacturing process • Expected dosage and route of administration
Expected indication	• Justification of significant benefit in Japan • Description of the target disease (summary of the cause and symptoms, prevalence of the condition, and justification as to why existing methods are not satisfactory) • Medical plausibility, including the mechanism of action and clinical data • Summary of current regulatory or development status, and marketing history outside Japan • Summary of current development status and plan of the product in Japan
Administrative information	• Details of the sponsor and contact details for the application • Submission date

accelerated. The report should include information on the current prevalence of the condition or the potential return on investment (as applicable based on the original ODD application), the current life-threatening or debilitating nature of the condition, the current existence of other methods for the diagnosis, prevention or treatment of the condition, and, if applicable, a justification of the drug's significant benefit. A template is available from the EMA website.[10] The orphan maintenance assessment report is subject to public disclosure, as it is included in the European Public Assessment Report (EPAR).

If EMA has already granted marketing authorisation and a period of market exclusivity for an orphan "similar medicinal product", an orphan similarity report must also be submitted.[10] A similar medicinal product is defined in Article 3 of Commission Regulation (EC) No 847/2000 as "a medicinal product containing a similar active substance or substances as contained in a currently authorised orphan medicinal product, and which is intended for the same therapeutic indication". The assessment of similarity is based on the principal molecular structural features of the product, the mechanism of action, and the indication. Even if a drug is assessed as being a similar medicinal product, marketing authorisation may also be granted for the same therapeutic indication under certain circumstances, including in cases where the second medicinal product can be shown to be safer, more effective, or otherwise clinically superior. In this case, a critical report justifying clinical superiority to the authorised product must be submitted. There are parallels with the "same drug" considerations for a US orphan drug application (see Subsection 3 in Table 3), although any information already used for that purpose may need to be updated and adapted for the EU rather than the US.

Close collaboration with clinical science and regulatory affairs is necessary to ensure that the core messaging is up to date and in line with the rare disease/orphan drug possibilities offered in the applicable jurisdiction.

Additional peri-approval documents for orphan drugs

Before applying for marketing authorisation, a briefing package may be developed to specify which type of application or regulatory pathway the sponsor believes is the most appropriate, considering the epidemiology of the disease in the region of interest, the existing treatments, and the pathways available in the region.

The rationale for selecting a particular type of application or regulatory pathway may also be required as part of the responses to the questions received during the assessment of a marketing application by the agency. The selected regulatory strategies may also evolve over time as new data from clinical trials become available. Close collaboration with clinical science and regulatory affairs is necessary to ensure that the core messaging is up to date and in line with the rare disease/orphan drug possibilities offered in the applicable jurisdiction.

After authorisation

Approval of orphan drugs may be granted with limited data on safety and efficacy via routes such as accelerated marketing approval (FDA), or conditional marketing authorisation or approval under exceptional circumstances (EMA). After authorisation, however, regulatory agencies may require the marketing authorisation holder to conduct additional postmarketing studies and clinical trials that provide confirmatory information on the efficacy, safety, pharmacokinetics/pharmacodynamics or use in special populations.

Marketing authorisation holders are required to report the status of these studies annually. While FDA uses Form FDA 3989[11] to facilitate the submission and ensure consistency of annual status reports, EMA requires a clinical overview addendum (COA) among other documentation.[12] Medical writers often drive development of the COA, the clinical summaries, and the reports that summarise the results from the studies conducted to accomplish the agency requirements. Similarly to other regulatory documents, collaboration and early planning are essential to effectively develop these documents. Medical writers should work closely with other functions from document conception to ensure that the statistical outputs and the associated messages enable a critical evaluation of the status of fulfilment of the agency requirements. Furthermore, thorough planning allows the re-

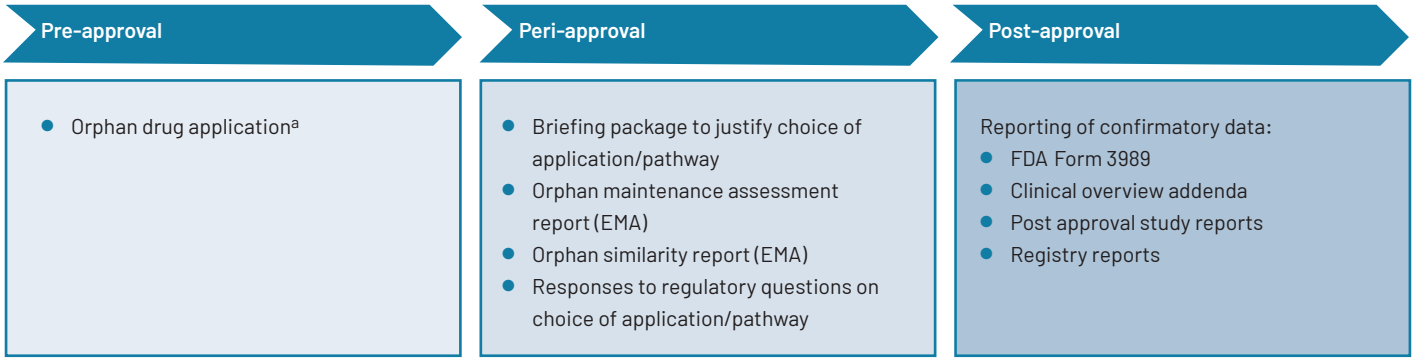

Figure 1. Overview of documents in orphan drug development

Abbreviations: EMA, European Medicines Agency; FDA, Food and Drug Administration.

[a] In the United Kingdom, orphan drug designation can only be requested at the time of marketing application.

purposing and reuse of content among documents.

Summary

Medical writing for a rare disease indication for which orphan drug status is sought requires several additional document types to those required in traditional drug development pathways. Regional variations in process and requirements can pose challenges; however, careful planning, judicious reuse of material, and close collaboration with other functions ensures success and ultimately addresses unmet needs in patients, which is extremely rewarding.

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Disclosures and conflicts of interest

The authors declare no conflicts of interest.

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